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DRUG DISCOVERY

Inter-arm Systolic Blood Pressure Difference of 15 mm Hg and its Relationship to CRP and other Cardiovascular Risk Markers

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ABSTRACT

Blood pressure is generally measured on in one arm – usually the non-dominant arm. However, increasing data suggests that arm to arm difference in blood pressure is common and may indicate atherosclerotic peripheral vascular disease. Other causes of inter-arm blood pressure difference include vasculitis, fibromuscular hyperplasia, connective tissue disorders, radiation arteritis, thoracic outlet compression, dissecting aortic aneurysm, and congenital abnormalities. Its presence is therefore not benign. The common etiology of this abnormality has been attributed to atherosclerosis involving the subclavian arteries. It also is a proxy for generalized atherosclerotic disease. A recent meta-analysis of 20 studies revealed that a systolic blood pressure difference of more than 15 mm Hg between the right and left arm was associated with a 2.5 greater risk of peripheral vascular disease, a 1.7 fold increase in cardiovascular mortality, and a 1.6 higher risk of all-cause death. Atherosclerosis is associated with vascular inflammation. CRP is a sensitive and reliable biomarker of this phenomenon and is frequently found elevated in patients with systolic inter-arm blood pressure difference.

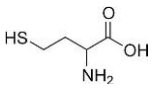
Key words: hypertension, CRP, inflammation, atherosclerosis, interarm blood pressure difference

Abbreviations: CRP: C-reactive protein, hsCRP: high sensitivity C-reactive protein, SIAD: Systolic inter-arm blood pressure difference of more than 15 mmHg, BP: blood pressure, HTN: hypertension, JNC7: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, ASH: American Society of Hypertension, TC: total cholesterol, LDL: low density lipoprotein cholesterol, HDL: high density lipoprotein cholesterol, NIAD, no inter-arm blood pressure difference.

1. INTRODUCTION

Inter-arm difference (SIAD) in systolic blood pressure (BP) of more than 15 mm Hg is not uncommon. It is attributed to atherosclerotic peripheral vascular disease involving the subclavian arteries. It is associated with increased mortality and a reduced event free survival. It is commonly seen in hypertensive patients. Hypertension is a common disease and has reached epidemic proportions worldwide. Overall, approximately 20% of the world's adults are estimated to have hypertension (Hajjar et al, 2006). Its prevalence dramatically increases in patients older than 60 years and approaches 50%. In 2001, approximately 54% of all strokes and 47% of all ischemic heart disease related deaths were attributable to systolic hypertension (Williams 2009). Hypertension related deaths are expected to increase by over 60% by 2025, rising from 972 million to 1.56 billion worldwide (Kearney et al, 2005). It is responsible for approximately one half of the health burden and costs worldwide (Abegunde et al, 2007). The excessive and often premature morbidity and mortality associated with hypertension is reversible with lifestyle changes and anti-hypertensive treatment. Clinical trials have shown that treating hypertension reduces the risk of stroke by 35% to 40%, the risk of heart attack by 20% to 25%, and the risk of heart failure by more than 50%. There is reduced renal failure and a decrease in premature cardiovascular death - an increase in lifespan (Veterans Administration Cooperative Study Group, 1972, Australian National Blood Pressure Study, 1980, MRC Working Party 1985, SHEP Cooperative Research Group. 1991). In spite of this compelling data, extensive research and widespread patient education, 30% of the adults are still unaware of their hypertension, 40% are not receiving treatment and almost 67% of the treated hypertensive patients not achieving a treatment goal of bringing the blood pressure to less than 140/90 mm Hg (Chobanian et al, 2003). The dismal rates of control are due to several factors including socioeconomic (inability to obtain healthcare or medications), methodological (improper blood pressure measurement), diagnostic (white coat hypertension), noncompliance (both lifestyle modification and medication) and therapeutic (inadequate treatment). Inter-arm blood pressure difference is another cause of poor control, as the higher uncontrolled blood pressure may be missed, not only for the initial diagnosis but also during subsequent visits following initiation of treatment (Clark et al, 2012). More ominously, it has been noted to be associated with increased morbidity and mortality. Although various mechanisms may be responsible, underlying atherosclerotic obstruction is the usual cause in inter-arm blood pressure differences of more than 15 mm in treated hypertensive patients. Increased atherosclerosis is associated with elevated CRP – a sensitive marker of inflammation. Our study looked at various laboratory measured cardiovascular markers/risk factors for atherosclerosis, including CRP in a cohort of hypertensive patients with SIAD.

Homocysteine:



It is a non-protein amino acid biosynthesized from methionine. Increased levels in the blood are associated with cardiovascular disease

2. METHODS

We reviewed the charts of 106 consecutive hypertensive patients seen during a period of four weeks for follow up visits. Standard blood pressure measurement techniques were used with an appropriate-sized cuff at the level of the right atrium, with the patient rested for 5 minutes, and with the back supported. As part of the study, blood pressure was measured in both arms using the same sphygmomanometer during the same sitting. Systolic blood pressure was categorized as follows: Normal: less than 120/80 mmHg, Pre-HTN: 120 to 139/80 to 89 mmHg, HTN: 140/90 mmHg or greater: Stage 1: 140 to 159/90 to 99 mmHg, Stage 2: 160/100 mmHg or greater. All patients had been diagnosed with hypertension with at least 2 consecutive elevated BP measurements (≥140 mm Hg systolic and/or 90 mm Hg diastolic or ≥130/80 mm Hg in the presence of diabetes mellitus or chronic kidney disease). All patients were on lifestyle changes recommendations and conventional anti-hypertensive patients, consistent with JNC 7 (Chobanian et al, 2003) and ASH guidelines (Gradman et al, 2010). All patients had blood work done within three months. Laboratory testing was done by credentialed free standing laboratories. The following biomedical markers were evaluated: Total cholesterol, LDL cholesterol, HDL cholesterol, hsCRP, homocysteine, uric acid and vitamin D. Laboratory values were considered abnormal as follows: TC (total cholesterol) >200 mg/dl, LDL (low density lipoprotein) >130, HDL (high density lipoprotein) <40, hsCRP (C-reactive protein) >3 mg/L and less than 10 mm/L, Homocysteine >15 umol/L, HbA1c >5.7, Uric Acid >7.2 mg/d and Vitamin D <30 ng/mL.

Uric acid:

Uric acid is a product of the metabolic breakdown of purine nucleotides. High blood concentrations of uric acid can lead to gout. High levels may be linked with hypertension and cardiovascular disease

3. RESULTS

Of the 106 (66 male, 40 female) patients with hypertension (ages: 23 to 92), 72 (68%) had no inter-arm BP difference (NIAD) and 34 (32%) had systolic inter-arm BP difference of more than 15 mmHg (SIAD). The cardiovascular biomarkers were abnormal as follows: TC: NIAD 36 (50%), SIAD 15 (44%), LDL: NIAD 18 (25%), SIAD 10 (29%), HDL: NIAD 18 (25%), SIAD 10 (29%), Homocysteine: NIAD 11 (15%), SIAD 6 (18%), HbA1c: NIAD 51 (71%), SIAD 25 (74%), Uric Acid: NIAD 15 (21%), SIAD 9 (26%), Vitamin D: NIAD

- An inter-arm difference in systolic blood pressure is not benign and has clinical implications.
- CRP is elevated in patients with an inter-arm difference in systolic blood pressure indicating chronic low grade vascular inflammation.
- An inter-arm difference in systolic blood pressure is associated with an increased risk of cardiovascular and all cause mortality over 10 years
- Blood pressure measurement in both arms should become a routine part of cardiovascular assessment in medical care.

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63 (88%), SIAD 28 (82%), CRP: NIAD 24 (33%), SIAD 18 (53%).

4. DISCUSSION

Blood pressure is generally measured on in one arm – usually the non-dominant arm. However, increasing data has suggested that routine readings should be done with both arms due to a not uncommon variation in arm-to-arm blood pressure differences. In a cohort of elderly patients, 10% of the patients had an inter-arm difference of 10 mm/Hg or greater (Fotherby et al, 1993). Lane found that 20% of his patients registered this difference (Lane et al, 2002). Another study of ambulatory patients demonstrated a 40% incidence of a 10-mm/Hg gradient in blood pressure between the right and left arms (Cassidy et al, 2001). Although a 10 mm Hg difference in inter-arm blood pressure is suggestive of peripheral vascular disease, a 15 mm or higher difference appears to be more ominous (Christopher E Clark et al, 2007). In a recent meta-analysis of 20 studies, a systolic blood pressure difference of more than 15 mm Hg between the right and left arm was associated with a 2.5 greater risk of peripheral vascular disease, a 1.7 fold increase in cardiovascular mortality, and a 1.6 higher risk of all-cause death (Clark et al, 2012).

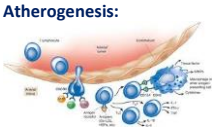
4.1. Causes of inter-arm blood pressure difference

Inter-arm blood pressure difference may be as a result of several conditions causing vascular obstruction, including atherosclerosis, vasculitis, fibromuscular hyperplasia, connective tissue disorders, radiation arteritis, thoracic outlet compression, dissecting aortic aneurysm, and congenital abnormalities (Osler 1915, Geisbock, 1905, Norris, 1917) Clinically common inter-arm blood pressure difference is probably due to stenosis involving the subclavian arteries (Shadman et al, 2004), and is related to atherosclerosis (Kay et al, 1930). Atherosclerosis is closely related to vascular inflammation. CRP is a reliable and sensitive test to measure this phenomenon.

4.2. Role of C-reactive protein

C-reactive protein (CRP) is an acute phase reactant and a sensitive, non-specific systemic marker of inflammation (Pepys et al, 2003). Its levels increase dramatically in response to severe bacterial infection, physical trauma, and other inflammatory conditions (Pepys, 1981), lower levels of CRP rise have been implicated with chronic inflammation in cardio and cerebro- vascular diseases (Ridker et al, 2000) and associated with traditional cardiovascular risk factors (Miller et al, 2005) and an increased risk of myocardial infarction and stroke in otherwise healthy individuals (Ridker et al, 1997, Koenig et al, 1984, Kuller et al, 1996). Its measurement may be a prognostic marker after an acute cardiac event Elevated plasma CRP concentrations are also associated with an increased risk of cerebrovascular events and an increased risk of fatal and nonfatal cardiovascular events in ischemic stroke patients. The mechanism appears to be mainly chronic low grade inflammation related vascular atherogeneis (Tracy et al, 1997). CRP level measurement is a good biomarker of low grade chronic vascular inflammation. It is related subclinical atherosclerosis as it is a sensitive indicator of inflammation and unaffected by hormones and anti-inflammatory drugs (Pepys 1981, Kindmark, 1972) the levels remain stable over a period of time) and it is an easily available and inexpensive (Macy et al, 1997). The inter-arm difference in systolic blood pressure in our patients is probably related to localized atherosclerotic subclavian obstructions and hence the significant association with elevated CRP in these patients. The atherosclerotic vascular process however is also generalized, as evidenced by an increase in overall cardiovascular and cerebrovascular morbidity and mortality in these patients.

Atherogenesis:



The development of atherosclerotic lesions in the walls of the arteries

5. CONCLUSION

Systolic inter-arm blood pressure difference of more than 15 mmHg is associated with peripheral vascular disease, pre-existing cerebrovascular disease, increased cardiovascular mortality and all-cause mortality. There was no difference in the presence of cardiovascular risk markers in our hypertensive patients with or without SIAD, except for CRP. CRP was elevated in disproportionately more patients with IAD. This supports the strong role played by inflammation in the development of atherosclerosis and the resultant SIAD in these patients. Presence of elevated CRP in patients with SIAD should be considered as a marker of a more severe and a more generalized atherosclerosis, necessitating a more aggressive approach. These data also make a compelling case for bilateral brachial blood pressure measurement to be incorporated into future guidelines for assessment and management of hypertension in individuals. The higher of the two readings should be used in the clinical management of hypertension (Singer et al, 1996).

SUMMARY OF RESEARCH

C-reactive protein is a marker of low grade vascular inflammation. Our study shows that this biomarker is often elevated in patients with systolic interarm blood pressure difference. This gives credence to the theory of an atherogenic process leading to obstruction - as the

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pathologic process behind this blood pressure difference. Being a proxy for generalized atherosclerosis, it also explains the increased cardiovascular and cerebrovascular morbidity and mortality in these patients.

FUTURE ISSUES

1. Can aggressive therapy reduce this inter-arm blood pressure difference?
2. Could objective reduction of inter-arm blood pressure difference in hypertensive patients be a prognostic indicator for future reduction in morbidity and mortality?

DISCLOSURE STATEMENT

The authors have no conflicts of interest to disclose.

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